REMARKS

The remainder of this Amendment is set forth under appropriate subheadings for the convenience of the Examiner.

Interview Summary

Applicant' representatives would like to thank the Examiner for conducting the telephonic interview on November 15, 2005 and for helpful suggestions. The Examiner's suggestions have been incorporated as discussed below.

Status of Claims

Withdrawn Claims 1, 24, 47 and 66 are canceled to expedite prosecution of the application. Claims 2, 6-10, 12-23, 25, 29-33, 35-46, 48, 52-65, 67, 71-77, 79-97 are now pending in this application. Applicant reserves the right to continue to prosecute any or all of the subject matter of canceled claims in continuing applications.

Amendments to the Claims

Independent Claims 2, 25 and 67 have been amended to make clear that the substituted or unsubstituted sterically hindered primary aliphatic amine is contained within the aqueous basic solution. Independent Claim 48 has been amended to make clear that *t*-butylamine is contained within the ammonium hydroxide solution. Claims 2, 25, 48 and 67 have been further amended to replace the term "cleavage" with "removal" to be consistent with the use of the term "remove" as recited in the claims. Support for these amendments can be found in Claims 2, 25, 48 and 67 themselves, *i.e.*, in the phrase "under conditions sufficient to remove ... β-cyanoethyl protecting group" and throughout the specification.

Rejection of Claims 2-6, 8-10, 14, 15, 18-22, 25, 31-33, 37-45, 48, 52, 54-64, 71, 72, 75-77, 79, 81, 82 and 85-97 under 35 U.S.C. § 102(b)

A. Summary of the Rejection

Claims 2-6, 8-10, 14, 15, 18-22, 25, 31-33, 37-45, 48, 52, 54-64, 71, 72, 75-77, 79, 81, 82 and 85-97 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Sinha, *et al.*, *Nucleic Acids Research, 12*: 4539-4557 (1984) (hereinafter "Sinha, *et al.* ") for the reasons described in the previous Office Action dated January 7, 2005. Although there is no indication in the Office Action about patentability of independent Claim 67, Applicant presumes that this 102(b) rejection is also applied to independent Claim 67 in view of the rejection of its dependent claims, e.g., Claims 71, 72, 75-77, 79, 81, 82 and 85-97.

B. Applicant's Invention

Applicant's invention of independent Claims 2, 25, 48 and 67, as currently amended, employs an aqueous, basic solution that comprises at least one sterically-hindered primary aliphatic amine for substantially preventing modification of a β-cyanoethyl protected oligonucleotide or oligonucleotide analog during removal of at least one β-cyanoethyl group from the oligonucleotide or oligonucleotide analog. In particular, the method of independent Claim 48 utilizes an ammonium hydroxide solution (an aqueous basic solution) that comprises *t*-butylamine (a sterically-hindered primary aliphatic amine). That is, Applicant's invention employs an ***aqueous, basic*** solution ***combined with*** at least one ***sterically-hindered aliphatic amine***, such as *t*-butylamine, for removal of β-cyanoethyl protecting group.

C. Applicant's Invention Is Novel in view of Sinha, *et al.*

The Examiner believed that Sinha, *et al.* disclose the use of "concentrated aqueous ammonia using hindered primary amine." However, as discussed in the telephonic interview, there is no disclosure or suggestion anywhere in Sinha, *et al.*, including the Abstract of Sinha, *et al.*, of the use of "concentrated aqueous ammonia using hindered primary amine" referred to by the Examiner in the Office Action. The Abstract of Sinha, *et al.* is reproduced below (emphasis original):

> Various 5'-O-N-protected deoxynucleoside ... are favoured. Cleavage of the oligonucleotide chain from the polymer support, N-deacylation and deprotection of β-cyanoethyl group from the phosphate triester moiety can be performed in one step with concentrated aqueous ammonia. Mixed oligodeoxynucleotides are characterized by the sequencing method of Maxam and Gilbert.

As clearly stated above, there is no disclosure or suggestion at all in the Abstract of Sinha, *et al.*, nor is it disclosed anywhere in Sinha, *et al.*, of the use of concentrated aqueous ammonia combined with a hindered primary amine for removal of β-cyanoethyl group.

Sinha, *et al.* disclose cleavage of an oligonucleotide from a polymer support, deacylation and deprotection of β-cyanoethyl group in one step with concentrated aqueous ammonia alone, as referred to in the Abstract of Sinha, *et al.* Also, Sinha, *et al.* disclose a two-step process for cleavage of an oligonucleotide from a polymer support, deacylation and deprotection of β-cyanoethyl group. The two-step process employs *t*-butylamine (*t*-$BuNH_2$) in pyridine (non-aqueous) at the first step for the removal of β-cyanoethyl group, and then concentrated ammonia at the subsequent second step for the N-deacylation and cleavage from the polymer support. For example, page 4546 of Sinha, *et al.* state (emphasis added):

> The deprotection, in our synthetic strategy with the β-cyanoethyl group as phosphate protection, may be achieved: ***either*** by stepwise deprotections, where ***t-BuNH$_2$/Pyridine (or Et$_3$N/Pyridine) mixture is used for the removal of β-cyanoethyl group***, followed by N-deacylation and cleavage from the polymer with conc. aq. NH_3 ***or*** one step deprotections by ***conc. aq. NH$_3$ alone***.

Therefore, Sinha, *et al.* do not teach removal of β-cyanoethyl protecting group using an aqueous basic solution that contains at least one sterically-hindered aliphatic amine. As such, independent Claims 2, 25, 48 and 67 of the application are novel in view of Sinha, *et al.* Claims 3-6, 8-10, 14, 15, 18-22, 31-33, 37-45, 52, 54-64, 71, 72, 75-77, 79, 81, 82 and 85-97 are dependent from independent Claims 2, 25, 48 and 67 directly or indirectly, and thus these claims are also novel in view of Sinha, *et al.* Applicant respectfully requests reconsideration and withdrawal of this rejection.

Rejection of Claims 2, 6, 7-10, 14, 15, 18-22, 25, 31-33, 37-45, 48, 52-65, 71, 72, 75-77, 79, 81, 82, 85-97 under 35 U.S.C. § 103(a)

Claims 2, 6, 7-10, 14, 15, 18-22, 25, 31-33, 37-45, 48, 52-65, 71, 72, 75-77, 79, 81, 82, 85-97 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Sinha, *et al.* in view of U.S. 6,465,628 B (hereinafter "Ravikumar, *et al.*")

As discussed above, Applicant's invention employs an aqueous, basic solution combined with at least one sterically-hindered aliphatic amine (e.g., *t*-butylamine) for substantially preventing modification of a β-cyanoethyl protected oligonucleotide or oligonucleotide analog during removal of at least one β-cyanoethyl protecting group from the oligonucleotide or oligonucleotide analog.

Sinha, *et al.* do not teach a process for removal of β-cyanoethyl protecting group using an aqueous, basic solution combined with at least one sterically-hindered aliphatic amine, as discussed above. Moreover, Sinha, *et al.* do not teach that the use of an acrylonitrile scavenger in an aqueous, basic solution can substantially prevent modification of a β-cyanoethyl protected oligonucleotide or oligonucleotide analog during removal of β-cyanoethyl protecting group. Also, Sinha, *et al.* does not teach that sterically-hindered aliphatic amines, such as *t*-butylamine, would have any acrylonitrile scavenging properties.

Ravikumar, *et al.* disclose the use of a certain amine, either by itself or in an organic solvent (see, for example, column 13, lines 43-52 and Example 22 of Ravikumar, *et al.*) for deprotection of oligonucleotides. However, as with Sinha, *et al.*, Ravikumar, *et al.* do not teach a process for removal of β-cyanoethyl protecting group using an aqueous, basic solution combined with at least one sterically-hindered aliphatic amine. Moreover, none of the amines disclosed in Ravikumar, *et al.* are sterically-hindered primary aliphatic amines. The only primary aliphatic amine contemplated by Ravikumar, *et al.* as a possible acrylonitrile scavenger is a non-hindered *n*-butylamine which is structurally distinct from the sterically-hindered *t*-butylamine of Sinha, *et al.*

Therefore, there is no suggestion or teaching in either Sinha, *et al.* or Ravikumar, *et al.* that would motivate one of ordinary skill to employ an aqueous, basic solution that comprises at least one sterically-hindered primary aliphatic amine for removal of β-cyanoethyl protecting group.

Accordingly, Claims 2, 6, 7-10, 14, 15, 18-22, 25, 31-33, 37-45, 48, 52-65, 71, 72, 75-77, 79, 81, 82, 85-97 would not have been obvious to one of ordinary skill in the art in view of Sinha, *et al.* and Ravikumar, *et al.*, taken either separately or in combination. Applicant respectfully request reconsideration and withdrawal of this rejection.

CONCLUSION

In view of the above amendments and remarks, it is believed that all pending claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Doreen M. Hogle
Doreen M. Hogle
Registration No. 36,361
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
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